NON-SPECIFIC URETHRITIS*

IS MYCOTIC INFECTION IMPORTANT?

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The editorial of a recent number of the *British Journal of Venereal Diseases* (1953) stressed the problem of non-specific urethritis.

The prevalence of the disease was noted, namely 10,794 new male cases in 1951 compared with 14,975 new male cases of gonorrhoea. Mention is then made of the possibility of a virus, and of organisms of the pleuropneumonia group being the cause. In conclusion it is stated :

> this subject is full of unsolved problems . . . the key to knowledge is the discovery of the causative organism on which all depends. Here then is the challenge of a neglected major problem, an insidious, highly prevalent and perhaps incurable disease, which is the source of much more ill health and unhappiness than is generally suspected. Surely there is the strongest possible case for an organized investigation into this condition with adequate financial support in which bacteriologists and clinicians should combine their resources.

We are in full agreement with this opinion, and the purpose of this paper is to draw attention to one aspect of the disease, namely the possibility that fungus elements found in urethral and prostatic secretions and in urine may indicate that mycotic urethritis is far more common than was previously supposed.

Incidence

The period under detailed review is 1 year at a single V.D. clinic in Manchester. In that time the number of new male attendances was 722, of which 120 were suffering from gonorrhoea. The corresponding female figures were 475 and 81. Of the cases not suffering from gonorrhoea, 30 males and 55 females showed microscopical evidence of fungus elements in urethral, prostatic, or cervical secretions, or in the urine. In addition six males had gonorrhoea and fungus. The incidence, therefore, of this finding was : male 5 per cent. of all new attendances, and female 11·6 per cent. of all new attendances. Thus one in twenty of all new male attendances and over one in ten of all female attendances exhibited in the genito-urinary tract some evidence of fungus infection. It is not proposed to comment in any further detail on the female cases, as it is well known that such a state of affairs has existed for a very long time, and many patients do not attend V.D. clinics but are seen and treated in gynaecology and dermatology departments. The incidence of male cases, however, may appear startling when it is remembered that as a rule only single case reports are to be found in the literature, and Harkness (1950a) devotes only five pages to fungi out of a total of 395. In order to confirm our figures, the number of cases showing fungus elements during a 4-year period was noted, and it was found that these totalled 134 male cases, indicating that the average was being maintained. These 4 years (including the detailed year) occurred since the introduction of antibiotics for the treatment of gonorrhoea and other diseases.

Clinical Features of 36 Male Cases

The ages of the men ranged from 22 to 63 years (average 32), the majority being in their early thirties. Twenty were single, fifteen married, and one was a widower. An attempt was made to discover whether they had received antibiotic treatment before the discovery of the fungus, but this was not easy and was of doubtful accuracy. Some did not know the nature of injections they had received for the present illness or for previous attacks or for other illnesses ; some did not know the nature of tablets or capsules given for similar reasons ; and some may well have given false information or have forgotten. Despite this, it is perhaps worth recording that nineteen stated they had not received any antibiotic treatment at any time and that seventeen admitted that they had. The duration of symptoms varied from one week to several years, and sixteen stated that they had had more than one attack. Six did not complain of any symptoms, and the fungus elements were found in routine examination of urethra, prostate, or urine

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during follow-up after treatment for gonorrhoea. This often occurred on the first and only visit after treatment and was followed by immediate default. No case of diabetes was found and only one case gave a history of joint disease. He had suffered from recurrent attacks of urethritis and dysuria for twenty years, and had had two attacks of pain in the joints during that time. He was seen in the Rheumatism Research Centre where a diagnosis of generalized osteo-arthritis was made.

The thirty patients who complained of urethral discharge almost all had anxious, worried expressions and described the discharge as clear, white, or yellowish. No exotic colourings (pink, red, or black) such as have been reported by Castellani (1929) were seen. Occasionally there was a greyish tinge and at times the discharge had the appearance of frank pus similar to that seen in gonorrhoea. Pain and burning sensations during micturition were not infrequent, and one patient described a dragging sensation in the groins and flanks. Balanitis was seen twice, paraphimosis once, and a non-retractable prepuce once. Seven patients complained that the discharge was present only in the mornings, before the voidance of the early morning urine. There was no history of instrumentation in any of the cases.

Investigations

Blood.—All cases had negative Wassermann and Kahn reactions, including one case who had been treated for secondary syphilis 5 years previously. Over half had a gonococcal complement-fixation test performed, and these were all negative.

Urethral Smears.—These were taken in all cases direct on to the slide from the urethral meatus after preliminary cleaning with normal saline. The slides were fixed and stained with Gram. The fungus elements usually showed as Gram-positive but occasionally they failed to take up any stain. Pus cells, epithelial cells, and cellular debris were found in most smears. Coccal organisms and various bacilli were often seen, and occasionally the presence of a streptothrix (Fig. 1) gave an indication that a more thorough search should be made for the presence of fungal elements. Fungus was seen as either spores or mycelium or both. The spores varied in size, but were usually small, oval, budding, thin-walled, yeast-like cells staining Gram-positive. Mycelium was sometimes sparse and at other times in thick clumps. The hyphae varied in thickness and were sometimes in short chains and sometimes extended over several fields of the microscope objective. On two occasions raquet hyphae were seen (Figs 2 and 3). As a rule the mycelium stained Gram-positive, but Gram-negative types and some without any stain were seen. Such variations did occur on the same slide. Occasionally the hyphae had a granular appearance.

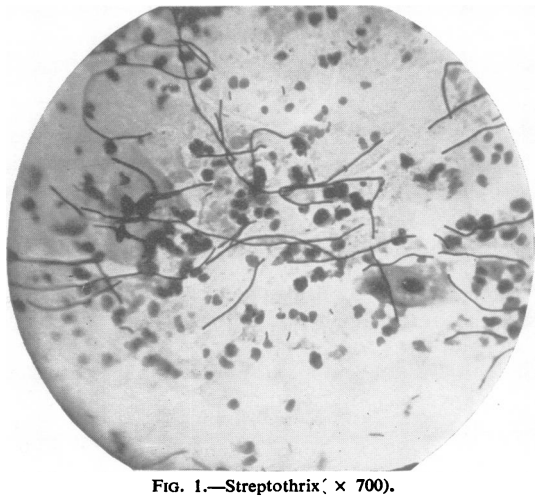

FIG. 1.—Streptothrix (× 700).

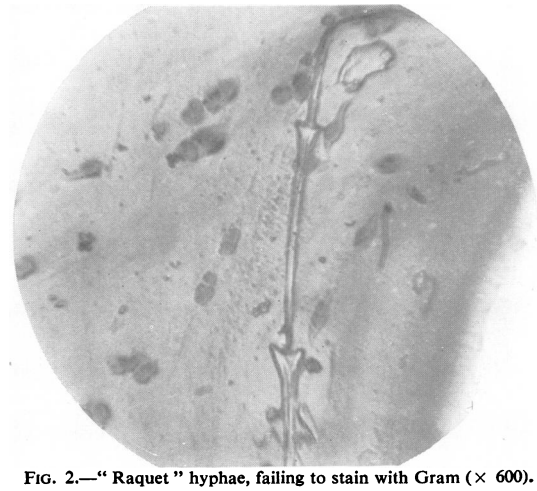

FIG. 2.—" Raquet " hyphae, failing to stain with Gram (× 600).

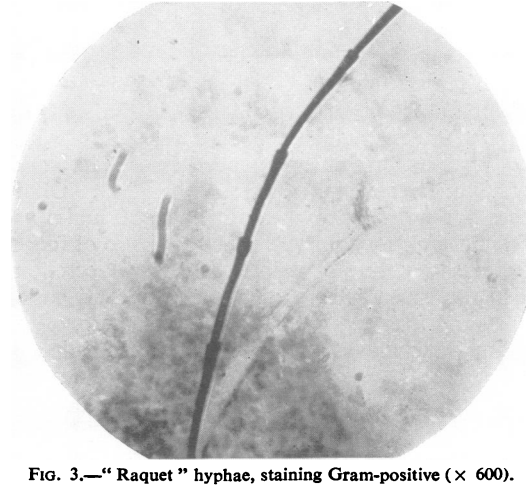

FIG. 3.—" Raquet " hyphae, staining Gram-positive (× 600).

Prostatic Smears.—These were obtained in the usual way.

Urine.—Very careful sterilization and cleaning of the glasses was undertaken.

Neat " Lysol " was first allowed to stand in the glasses for some minutes, they were then emptied and refilled with spirit. They were then drained and flamed over a Bunsen burner. They then stood inverted on a flamed filter paper and were ready for use except for a final rapid flaming immediately before the urine was passed into them.

The urine was examined immediately. In cases showing fungal elements, the following characteristics were usually found.

View clear with rapidly descending colourless particles reflecting light with the production of a glitter effect. In addition there were usually white threads which descended rapidly or slowly to the bottom of the glass, forming a deposit. These threads or some of the deposit could be easily removed with a platinum loop and when examined microscopically often revealed spores or mycelium or both.

In suspected cases, when the first examination of urethral secretion and urine was negative, the urine glass was covered with a flamed filter paper and the urine was examined at 24, 48, and 72-hour intervals. Sometimes positive findings resulted, and in other cases the urine remained negative, but when further specimens were taken from the same patient at a later date they were positive. The criticism of outside contamination is answered by an experiment with controls.

Twelve men, after treatment for gonorrhoea with penicillin and sulphonamides, had their urine collected in the manner described. These urines were examined daily for up to 8 days and none showed any microscopic evidence of fungus. In another control experiment, eighteen volunteers including medical students and staff had their urine examined in a similar way, some specimens being kept for 12 days, and all were negative.

Of the 36 positive cases, fungus elements were found in urethral smears only in fifteen cases, in urine only in six cases, in prostatic secretion only in two cases, in urethra and urine (not necessarily at the same time) in twelve cases, and in prostate and urethra in one case.

Trichomonas.—At least half the cases were examined for this with entirely negative results.

Contacts.—In a large proportion of the cases it was not possible to correlate the findings by examination of suspected contacts. Some men denied exposure, some admitted exposure, but would not, or could not, persuade their partners to attend. Some admitted frequent exposures at different sources, but owing to our lack of knowledge of the incubation period of the disease, we could not trace the most likely source. Some, on learning that they were not suffering from gonorrhoea or syphilis, refused any further information. One case was of interest :

A husband attended with a urethral discharge in which fungus was found, and the history revealed that his child had been suffering from " thrush " 3 months previously. Later his wife had a vaginal discharge and cervical smears showed fungal elements which proved on culture to be *candida albicans.*

Many positive female cases told us that their consorts had, at intervals, suffered from non-specific urethritis.

Culture.—Numerous culture slopes of Sabouraud's glucose agar medium were inoculated with material from the urethra and urine in microscopically positive cases. A large number of different strains of fungi were grown. These included *candida albicans,* penicillium, white yeast (Fig. 4), and rhodotorula, aspergillus, *monilia sitophila, C. Krusei,* etc. Many of these were classified as contaminants by the mycologist. We feel confident that these were not airborne contaminants of the material being examined but would agree that it is arguable whether they were pathogenic or non-pathogenic. This controversial point is perhaps the whole crux of the problem. But, as we see it, a contaminant is only non-pathogenic so long as it has not been shown to be responsible for disease. It may be that these fungi are responsible for disease in the genito-urinary tract, and if so, a reclassification of pathogenic and non-pathogenic fungi will be necessary.

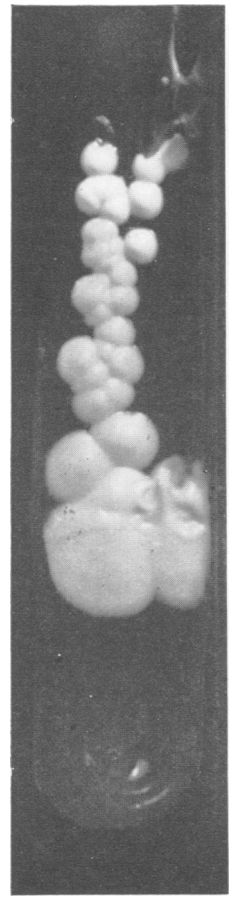

FIG. 4.—A 2-month culture of " white yeast " from male urethra.

Urethroscopy and Cystoscopy were not carried out.

TREATMENT

Attempts were made to eradicate the fungus in various ways.

Urine.—It was thought if the fungus was present in the bladder a change of *p*H might produce conditions unfavourable for the continued growth and multiplication of the organism. This was done by giving a mixture of gr. 10 acid sodium phosphate and gr. 10 hexamine three times daily or by giving *Mist. Pot. Cit.* B.P.C. 0·5 ounce three times daily, depending on whether the urine was acid or alkaline when the fungus was discovered.

Prostate.—In a few cases regular prostatic massage was performed when it was thought that the gland might be harbouring the fungus.

Urethra.—Substances of known fungicidal action were used for anterior and posterior urethral irrigation.

Potassium permanganate 1 in 8000 and oxycyanide of mercury 1 in 8000 daily were tried. Undecylenic acid and sodium undecylenate solutions in strengths of 0·3 per cent. and 0·5 per cent. respectively were used. A B.D.H. product known as " Gecophen " (*p* chlorophenyl, a glycerol ether) with proved fungicidal, non-toxic, and non-irritant properties was tried in a dilution of 0·3 per cent. A few cases also received sulphonamides and antibiotics (penicillin, streptomycin, and chloramphenicol).

Results

In some cases improvement did seem to follow a course of treatment with one or more of the above methods, but the cyclic nature of the condition made it difficult to assess results. It was not thought that any one regime or technique was superior to another.

Case Histories

The following are representative of the 36 cases.

Case 1, a single man aged 32, admitted coitus 3 weeks before. Duration of signs and symptoms 2 days. He complained of slight, whitish urethral discharge associated with a burning sensation in the penis during micturition, but no frequency. On examination he had a white mucoid discharge. Microscopy showed no gonococci, a few pus cells, and numerous epithelial cells. The urine was clear with a few threads falling slowly to the bottom of the glass. Microscopy of a thread showed fungus elements (Fig. 5). Wassermann reaction, Kahn, and gonococcal complement-fixation test were negative. He was treated with *Mist. Pot. Cit.* and his urethral discharge slowly diminished till all signs and symptoms were absent 6 weeks later.

Comment.—Microscopical evidence of fungi in urine only. Recovery probably spontaneous.

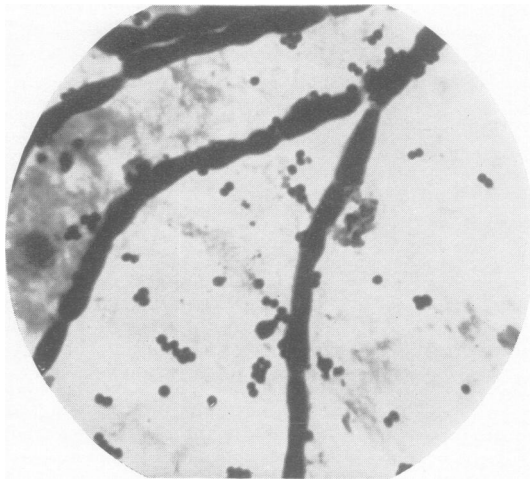

FIG. 5.—Case 1, mycelium and spores found in thread from urine (× 600).

Case 2, a single man aged 30, had suffered from gonorrhoea 3 years previously and had been treated with penicillin. He complained of yellowish discharge of 2 weeks' duration. He had had frequent exposures to infection. The urethral smear showed no gonococci but numerous pus cells. The urine was clear with many heavy threads falling rapidly ; immediate examination of one of the threads gave negative results, but 24 hours later microscopy of the deposit showed numerous pus cells and many spores. The clinical signs persisted despite treatment with streptomycin (given on the first day before the spores were found), acid sodium phosphate, and hexamine. Two months later a course of daily irrigations with Gecophen 0·3 per cent. was begun. After 1 week the urethral discharge was lessened but spores were still easily found in the urine (Fig. 6). After 2 weeks he was free from clinical signs and symptoms, and smears from the urethra, prostate, and urine were negative. Observation was continued for 6 further weeks, without sign of relapse.

Comment.—Apparent response to treatment with " Gecophen ".

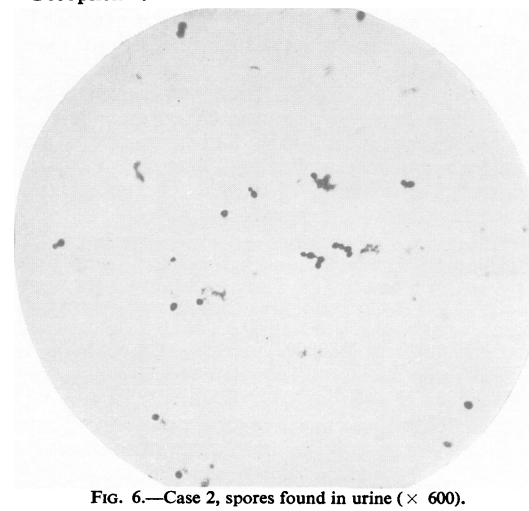

FIG. 6.—Case 2, spores found in urine (× 600).

Case 3, a married man aged 44, had been treated for " urethritis " while in the forces 6 years before. He complained of early morning " spot ", and denied extramarital risk. He had no pain or frequency. Direct smears from the urethra revealed spores and mycelium (Fig. 7, opposite).

He was treated with *Mist. Pot. Cit.* and one week later no fungus was found in a much reduced urethral discharge, but 2 weeks later the early morning discharge had returned and threads were easily seen in his urine. He was given daily irrigations of sodium undecylenate 0·5 per cent. for one week with apparent success, but a recurrence occurred 2 weeks later and was treated with acid sodium phosphate and hexamine with apparent good effects. His next relapse was treated with irrigations of oxycyanide of mercury 1 in 8000 and later with " Gecophen " 0·3 per cent. ; 3 weeks after completion of the last course of treatment his urethral smears still

showed fungus elements, but the clinical signs were diminishing, and 2 weeks later he had apparently completely recovered and was leading a normal married life.

Comment.—Fungal elements found repeatedly, apparent temporary response to many different treatments.

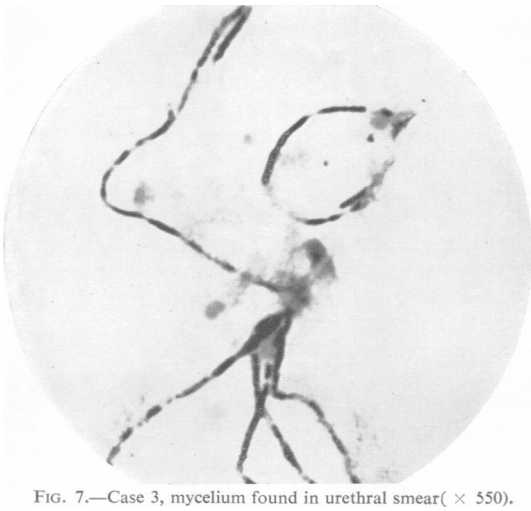

FIG. 7.—Case 3, mycelium found in urethral smear(× 550).

Case 4, a married Indian aged 31, complained of a thick yellow urethral discharge of 7 days' duration. Microscopy confirmed the diagnosis of gonorrhoea. He was treated with 300,000 units penicillin and 20 g. sulphatriad. A week later there were no clinical signs and the urethral smear showed no organisms, a few pus cells, and many epithelial cells. Three weeks later he again showed no clinical signs but the urethral smear revealed mycelium (Fig. 8). He then defaulted.

Comment.—A case showing the presence of fungus 3 weeks after treatment for gonorrhoea with penicillin. Symptomless and probably of transient nature only.

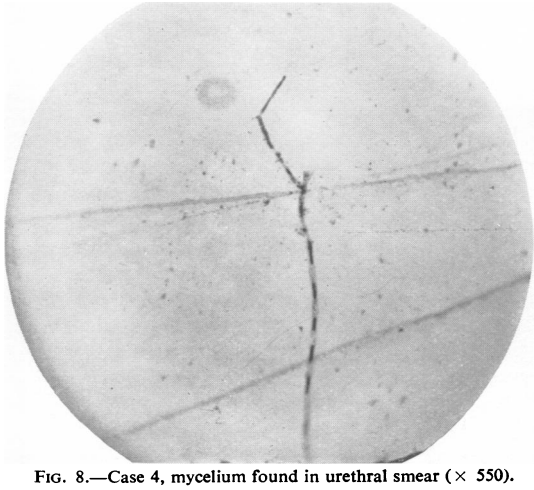

FIG. 8.—Case 4, mycelium found in urethral smear (× 550).

Case 5, a single man aged 30, complained of an intermittent urethral discharge for 6 years since treatment for gonorrhoea with penicillin, and denied recent exposure. Examination showed a white urethral discharge microscopically free from organisms but containing many pus cells. The urine was clear except for heavy threads in which spores and mycelium were easily found (Fig. 9); 2 weeks later, having been instructed to take his own specimen before voiding his early morning urine, he brought a slide which showed many fungal elements and spermatozoa. He was treated with acid sodium phosphate and hexamine and his condition improved greatly during the next 2 weeks. No further evidence of fungus was found during the next 2 months, but he complained of occasional slight early morning "spot". He then developed an acute gonorrhoea and defaulted after treatment with penicillin.

Comment.—A long-standing case of non-specific urethritis with evidence of fungal elements in the urine and urethral secretion.

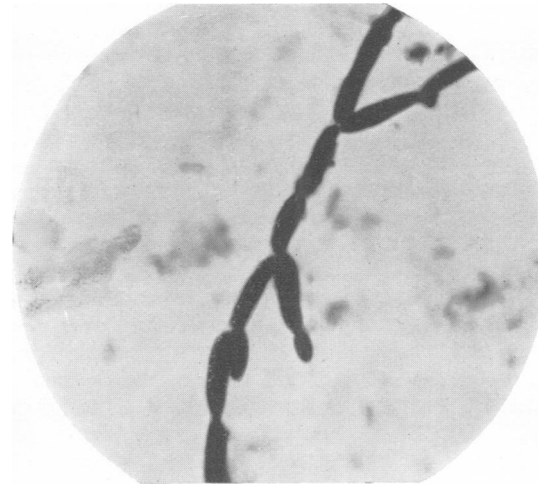

FIG. 9.—Case 5, mycelium found in heavy thread from urine (× 600).

DISCUSSION

The problem arising from these findings is how much significance to attach to the presence of fungus elements found in secretions from the male genito-urinary tract. We believe that their presence is very real and quite unmistakable once their existence is realized. With experience the history and clinical signs alone become sufficiently suggestive to cause a search to be made in the urine, and prostatic and urethral secretions. On the other hand, the chance finding of fungal elements in urethral secretions routinely examined during tests of cure after treatment for gonorrhoea often comes as a complete surprise. Some cases who have attended for advice on many occasions may show fungal elements only at infrequent intervals, which suggests that perhaps

the growth and multiplication are intermittent, depending on the presence of suitable conditions.

This feature is, of course, not unusual in fungus infections in other parts of the body, especially glabrous skin. Tinea pedis is often an intermittent disease, revealing itself as outbreaks of interdigital scaliness and peeling with long periods of complete freedom from clinical or microscopical evidence of fungus between the toes. Given suitable conditions of warmth, moisture, correct nutritional requirements, and absence of antagonistic bacteria, the fungus multiplies and gives rise to gross clinical signs and symptoms. It may well be that a similar sequence of events occurs in the genito-urinary tract, the fungi only making their presence felt when all the factors necessary for growth are present together. It is not always clear from many case histories why fungus elements are found at one time and not at another, although on occasions it seems reasonable to suppose that the administration of antibiotics has been the direct precipitating cause. In the other cases it is possible that the causative factor has eluded us because we are not yet fully aware of the conditions necessary for growth of fungi. Diabetes and glycosuria were well known causes in the pre-insulin era but these were absent from our series. Mycotic urethritis, too, was said to be commoner when instrumentation was a frequent practice, and it was thought that physical damage to the urethral lining was necessary before the disease developed. Nowadays instrumentation is rare, and none of the cases described in this paper had ever been subjected to catheterization or the passage of bougies, though a few had received urethral irrigation. In dermatology blame is sometimes attached to hyperidrosis and the seborrhoeic diathesis, but these conditions were found no more commonly than among the ordinary population. Another question is where in the genito-urinary tract the fungus originates? The use of the urethroscope and the cystoscope may provide the answer. Reports by Frei (1925), Preis and Forró (1928), and Pierangeli (1925) of single cases describe white patches seen in the anterior and posterior urethra. Harkness (1950b) states that the infection may descend from lesions in the upper urinary tract. Cases of fungus infection in the bladder have been reported by Rafin (1927), Moulder (1946), and Sauer and Metzner (1948), but urethritis was not a feature. Fungus disease of the kidney is also known (Lundquist, 1931), but again urethritis was absent.

Gilliam and Vest (1951) reported a case of fungus infection of the urinary tract by a *Penicillium* mould.

A man aged 56 passed balls of pink material at intervals for 8 years; his urine was persistently sterile (this they attributed to antibiotic activity of the penicillium mould) and the bolus gave a pure growth of the fungus.

These authors commented on the fact that even well-trained mycologists have little first-hand knowledge of fungi pathogenic to man, and they pointed out that of the 88,000 types of fungi only about thirty species are said to be pathogenic. Sauer and Metzner (1948) described a case of thrush infection of the bladder in a woman. They thought that the infection invaded the bladder by way of the urethra and mentioned that this may be more common than the literature would indicate, suggesting that because its occurrence is not generally appreciated its diagnosis may be readily missed.

We cannot answer the question whether fungal elements, when found, are necessarily the cause of the urethritis, but in the cases described no other cause was found. It might be possible to obtain volunteers who would allow cultures of *Candida albicans* or other fungi cultured from patients with urethritis to be inoculated into their genito-urinary tracts in an attempt to produce the disease artificially. A positive result might lead us to modify our present conception of contaminants and non-pathogenic fungi. Negative results would not necessarily exclude the possibility of mycotic urethritis due to the particular fungus used, as human susceptibility to fungus diseases varies so greatly. It is probable that the "soil" is more important in the development of the disease than the introduction of the causative agent to the tissues. Unfortunately, the incidence of cutaneous fungus disease in the cases described was not recorded, but a useful clue might be obtained if it could be shown that cases of mycotic urethritis were more susceptible than ordinary people to *T. pedis* and *T. cruris*.

Treatment presented another difficult problem. This is closely paralleled by the difficulty in treating human cutaneous tinea, especially in the feet, groins, and nails.

Here again individual susceptibility is probably the most important factor. Spontaneous diminution of clinical signs and relief of symptoms was often noted. Some cases also appeared to respond to irrigation with one or more of the antiseptic and fungicidal preparations. Others were helped by changing, or attempting to change, the *p*H of the urine, but it is difficult to assess the real value of such therapy. It is doubtful whether we discovered any really successful treatment, and it is probable that this will only come when it is known for certain where the fungus is lurking.

Contaminated staining solutions are mentioned by Janet (1929) and Harkness (1950a) as a mis-

leading reason for the finding of fungal elements during microscopy. This possibility was borne in mind throughout the period under review and was rigorously excluded.

If the incidence of fungus infection is, in fact, rising, some explanation must be found. The obvious thought is that the increasing use of antibiotics is responsible. It is now recognized that oral, intestinal, and sometimes broncho-pulmonary overgrowth of fungi has followed the administration of antibiotics (*Lancet*, 1951). This is thought to be due to interference and imbalance in the normal relationship between the flora in these parts of the body. Elimination of the sensitive organisms allows overgrowth of the insensitive organisms of which the fungi are the largest group (*Lancet*, 1952). In the cases described above some attempt was made to decide if there was a relationship between the giving of antibiotics and the development of non-specific urethritis, but only in the six cases where fungus elements were found routinely after treatment of gonorrhoea with penicillin could it be said that any relationship might exist. The amount of penicillin given for this disease is so small and of such short duration that, even in these cases, its significance is doubtful, and the finding was microscopical evidence only without clinical signs or symptoms. We know of no satisfactory explanation, unless it is that the world-wide use of antibiotics during the past 10 years is resulting in a general increased pathogenicity of fungi. It would appear that there is an increase in the incidence of mycotic urethritis. Harkness (1950a) quotes thirteen single cases by different authors, two papers describing two cases each, and one paper describing five cases. He adds three of his own. He insists (1950a, b) that the disease is rare, and stresses the importance of repeated findings of the fungus elements before a diagnosis of mycotic urethritis is made. In the cases reported here, six out of 36 were chance observations following treatment of gonorrhoea, and, being symptomless, could hardly be called " cases of urethritis ". The remainder, however (all seen in 1 year), all showed fungus elements on more than one occasion, and complained of symptoms, usually an intermittent urethral discharge.

Coutts (1948) states that " recent investigations suggest that fungus infections of the genito-urinary tract are far more prevalent than was formerly supposed ", and that " probably certain obscure conditions will eventually be proved due to them ". This opposite view is qualified by a reminder that some fungi may be purely saprophytic, and the mere finding of fungal elements does not necessarily mean that they are causing disease ; but no means of deciding this point is suggested. Nor can we offer a deciding test ; we prefer at this stage merely to draw attention to the presence of fungi, hoping, by stimulating interest in this aspect of non-specific urethritis, to encourage others to investigate the problem.

Summary

In 1 year fungal elements were found in the genito-urinary secretions of 36 men. In thirty cases these fungal elements were the only abnormality detected, and were thought to be responsible for the " urethritis ". It is suggested that mycotic urethritis is far commoner than has hitherto been thought, but much more investigation is necessary before the true significance of the findings is assessed.

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